

Adult asthma severity in individuals with a history of childhood asthma

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Background: Childhood asthma can have a range of outcomes in adulthood.

Objective: To identify clinical features and exposures associated with persistence and severity of childhood asthma in adulthood.

Methods: Eighty-five of 121 subjects previously enrolled in a study of immunotherapy for childhood allergic asthma (age 5-12 years) were re-evaluated with allergy skin testing, spirometry, and interviews about asthma symptoms and medications. These young adults (age 17-30 years; 74% male) all had moderate to severe childhood asthma. Adult asthma severity was scored by using a modified version of National Heart, Lung, and Blood Institute severity categories.

Results: Thirteen (15.3%) of 85 adult subjects were in remission despite persistent childhood asthma. Another 19 subjects (22.4%) had only intermittent asthma. The remaining 53 had persistent asthma, of whom 12 (14.1%) had mild asthma, 25 (29.4%) had moderate asthma, and 16 (18.8%) had severe asthma. Subjects in remission, compared with subjects with intermittent or persistent asthma, had lower total serum IgE in childhood (412 ng/mL vs 1136 ng/mL vs 968 ng/mL; $P = .02$) and fewer positive allergy skin tests (7 vs 9 vs 10 from panel of 18; $P = .02$). Subjects in remission also had milder childhood asthma, indicated by lower average daily medication usage scores (1.6 vs 3.5 vs 4.4; $P = .005$) and lower percentage of days on inhaled corticosteroids (13.7% vs 24.7% vs 40.9%; $P = .008$). No significant association was found between current asthma severity and childhood immunotherapy ($P = .46$).

Conclusion: The prognosis of childhood allergic asthma in adulthood is largely determined early in life. The degree of atopy appears to be a critical determinant of asthma persistence. (*J Allergy Clin Immunol* 2005;115:61-6.)

Key words: *Childhood asthma, asthma severity, atopy, adult asthma outcomes*

Abbreviations used

BMI:	Body mass index
CAS:	Childhood Asthma Study
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
PC ₂₀ :	Provocative concentration producing a 20% fall in FEV ₁

Childhood asthma may be self-limited and remit over time or may persist and worsen in adulthood. A subset of patients may improve only to relapse years later. Several longitudinal studies on the natural history of childhood asthma have documented this variability. Gerritsen et al¹ followed 100 asthmatic children (age 6-14 years) and reported that 43% still had asthma symptoms in early adulthood 20 years later. In an unselected birth cohort (N = 613), Sears et al² reported that 14.5% had self-reported, persistent wheezing from childhood to 26 years of age, 27.4% remitted, and another 12.4% appeared to remit but subsequently relapsed by the age of 26 years. Similarly, the Melbourne Asthma Study reported that only 30% of its original asthma cohort (N = 113) had outgrown childhood asthma by the age of 42 years.³ These studies indicate that childhood asthma can wax and wane with several different long-term outcomes.

To identify clinical features associated with persistence of childhood asthma into adulthood, we undertook the follow-up of a cohort of young adults with a history of physician-diagnosed moderate to severe childhood allergic asthma. As children (age 5-13 years), they participated in a randomized, placebo-controlled trial of immunotherapy for childhood asthma conducted from 1984 to 1994.⁴ During this trial period, subjects underwent extensive evaluation with repeated methacholine challenges, pulmonary function measurements, allergy skin testing, symptom diaries and questionnaires, and home dust sample analyses. We now report clinical characteristics and early predictors of adult asthma severity in this cohort of young adults.

METHODS

Study participants

The Childhood Asthma Study (CAS) was a double-blind, randomized, placebo-controlled trial designed to study the role of

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TABLE I. Severity classification of current adult asthma*

Class	Symptoms	Nighttime symptoms	PFT†	Medications
Asymptomatic	None	None	FEV ₁ and ratio >80% predicted	None
Mild intermittent	≤2/wk	≤2/mo	>80%	PRN bronchodilator only
Mild persistent	2-6/wk	>2/mo	>80%	Daily medications (≤400 μg/d inhaled corticosteroid or leukotriene inhibitor, and so forth) ± as-needed bronchodilator
Moderate persistent	Daily	Weekly	60% to 80%	401 to 800 μg/d inhaled corticosteroid ± other medications, including as-needed bronchodilator
Severe persistent	>1/d	>1/wk	<60%	801 to 2000 μg/d inhaled corticosteroid ± other medications

*Classification based on highest class in any category.

†Postbronchodilator spirometry while on current, stable medication regimen.

immunotherapy as an adjunct treatment of childhood allergic asthma.⁴ The 121 original study members, age 5 to 12 years at randomization, had moderate to severe asthma on the basis of symptoms and medication usage and were diagnosed and treated by a physician for at least 1 year before enrollment. Evaluations performed during the original study included daily medication-symptom diaries, home allergen analysis, allergy skin testing, and methacholine challenges with associated spirometry. The cohort had varied socioeconomic status, gender, and ethnicity. The primary study outcome was the daily medication usage score as a measure of disease severity. The original CAS showed no significant differences between placebo and active immunotherapy groups, with both groups' medication use and methacholine responsiveness declining similarly during the trial period.⁴ Other end points, including unscheduled doctor visits and total serum IgE, did not differ.

An attempt was made to enroll all 121 of the original participants. Reasons for nonparticipation in the current study included inability to contact the subject (N = 10), incarceration (N = 3), and death (N = 1). Twenty-two additional CAS subjects did not respond to the recall for unknown reasons. Exclusion criteria for the current study included other medical conditions known to affect pulmonary function. One subject was excluded because of severe kyphoscoliosis under these criteria.

Informed consent was obtained from the 85 subjects enrolled under a protocol approved by the Johns Hopkins Institutional Review Board. Subjects continued their usual medications.

Study design

During the adult evaluation visit, subjects underwent spirometry, inhalant allergy skin testing, and questionnaires regarding their interim medical history, asthma symptoms, and medications. Active asthma exacerbation or oral corticosteroid use in the past 30 days or active pulmonary symptoms were criteria for exclusion from testing on any given day.

Asthma severity was classified by using a modified version of the 1997 National Asthma Education and Prevention Program algorithm,⁵ adjusted to include current medications in determining disease severity (Table I). Postbronchodilator spirometry was used for severity categorization instead of prebronchodilator values to avoid overestimation of asthma severity and to improve reproducibility, as has been suggested by others.⁶ Subjects were categorized in the most severe category for which they qualified. Subjects with no asthma symptoms, normal pulmonary function (FEV₁ and FEV₁/FVC >80% predicted), and no medications for at least 1 year were categorized as being in remission. Subjects with intermittent symptoms, normal pulmonary function, and as-needed bronchodilator use only were categorized as having intermittent disease. The

remainder of subjects (mild, moderate, and severe persistent) were categorized as having persistent disease.

Height, weight, and body mass index (BMI = weight [kg]²/height [m]) were compared with age-specific and gender-specific general population norms derived from the Centers for Disease Control and Prevention 2000 Growth Charts for the United States.⁷

Pulmonary function tests

Childhood prebronchodilator spirometry was obtained in conjunction with methacholine challenges by using a Collins water-sealed spirometer (WE Collins, Braintree, Mass). Adult pulmonary function testing was performed following American Thoracic Society guidelines⁸ on a Collins dry-sealed spirometer (WE Collins). Both childhood and adult spirometry were adjusted for age, gender, ethnicity, and height by using National Health and Nutrition Examination Survey III normative data.⁹

Skin testing

Skin testing was performed by using a panel of 18 common perennial and seasonal allergens (ALK-Abelló, Round Rock, Tex). The skin testing was performed as previously described.⁴ Skin test responses were graded 1 to 4+ on the basis of the wheal diameter relative to the histamine (10 mg/mL) control.

Bedroom dust sample analyses

Bedroom floor and mattress dust samples were collected during the childhood clinical trial. Samples were quantitatively analyzed for the presence of major allergens from cockroach (Bla g 1), dust mite (Der p 1 and Der f 1), and cat (Fel d 1) by methods reported previously.¹⁰

Statistical analyses

One-way ANOVA was used for group comparisons of continuous variables among the 3 adult asthma severity groups. The Kruskal-Wallis test was used for comparisons of highly skewed variables, serum IgE, and methacholine PC₂₀, whereas the χ^2 test was used for comparisons of categorical variables across the 3 adult severity groups. All *P* values are reported as 2-sided, and values less than .05 were accepted as significant. Statistical analysis was performed by using SPSS 10.1 software (Chicago, Ill).

RESULTS

Subjects

Eighty-five of the 121 subjects from the original CAS were enrolled. The enrolled group did not differ from

TABLE II. Adult asthma severity and medication use

	Subjects, N	Inhaled steroids ± other medications	Daily medication other than steroids	As-needed bronchodilator only	No medications in past year
Asymptomatic	13	0	0	0	13
Mild intermittent	19	0	0	18	1
Mild persistent	12	3	4	5	0
Moderate persistent	25	16	2	6	1
Severe persistent	16	7	3	6	0

TABLE III. Prebronchodilator spirometry (means ± SDs) by severity categories

	N	FEV ₁ (% predicted)	FVC (% predicted)	FEV ₁ /FVC (%)	%Δ after bronchodilator
Asymptomatic	13	94.3 ± 9.9	106.1 ± 8.6	88.7 ± 7.5	7.6 ± 3.7
Mild intermittent	19	91.9 ± 14.5	106.7 ± 12.8	86.2 ± 10.0	9.8 ± 6.9
Mild persistent	12	87.9 ± 9.3	102.0 ± 10.3	85.6 ± 10.0	6.8 ± 4.5
Moderate persistent	25	79.6 ± 15.8	102.9 ± 14.8	77.8 ± 12.7	12.9 ± 10.0
Severe persistent	16	66.0 ± 18.0	87.8 ± 14.4	75.2 ± 15.5	12.3 ± 10.8

FVC, Forced vital capacity.

those not re-evaluated in mean age at recall, gender, ethnicity, socioeconomic status, childhood lung function, asthma severity or medication use, immunotherapy status, and methacholine responsiveness at the end of the clinical trial, as described elsewhere.¹¹ The subjects evaluated in adulthood were predominantly male (73.8%), with a mean age of 24 years (range, 18-30 years). The ethnic distribution was 54.8% white and 44.0% African American. Fifty percent of the subjects had received active immunotherapy in childhood. The mean time interval between the end of the clinical trial and initial adult assessment was 10.8 years (range, 8.0-15.6 years).

Asthma severity

Current asthma severity is shown in Table II. Thirteen (15.3%) of 85 subjects were considered to be in remission, reporting no asthma symptoms or medications in the past year and demonstrating a postbronchodilator FEV₁ >80% predicted. Nineteen subjects (22.4%) were categorized as having mild, intermittent disease. Twelve (14.1%) had mild, persistent disease, 25 (29.4%) had moderate, persistent disease, and the remaining 16 (18.8%) had severe, persistent disease. Mean prebronchodilator spirometry and bronchodilator reversibility are shown in Table III.

Childhood predictors of adult asthma severity

The relationships of childhood asthma severity and atopic features to current, adult asthma status are shown in Table IV. Subjects in remission had a lower level of total serum IgE (412 ng/mL vs 1136 ng/mL vs 961 ng/mL; *P* = .03) and fewer positive allergy skin prick tests (7 vs 9 vs 10 from a panel of 18 allergens; *P* = .02) in childhood compared with subjects with intermittent or persistent symptoms. These subjects also had lower daily medication usage scores (1.6 vs 3.5 vs 4.4; *P* = .005) and a lower

percentage of days on inhaled corticosteroids (13.7% vs 24.7% vs 40.9%; *P* = .008) while in the original trial (Fig 1). Childhood immunotherapy status, methacholine responsiveness, and FEV₁ did not differ among the groups.

No statistically significant associations were found between adult asthma severity and several early risk factors and exposures, including prematurity at birth, breast-feeding, other children living in the same household, pets, family history, and secondhand tobacco exposure (Table V). Multinomial logistic regression analysis of adult asthma severity in relation to early risk factors also did not show any significant associations (data not shown).

Allergen analysis was performed during the childhood clinical trial phase of the study on bedroom dust samples. Childhood skin test sensitivity to cockroach was associated with higher levels of Bla g 1 allergen in the bedroom dust samples (*P* = .02), as has been previously reported.¹² A similar relationship between skin test sensitivity and exposure level was found for house dust mites (*P* = .03), but not for cat allergen (*P* = .31). No significant associations were found between specific allergen levels in settled dust for subjects with a positive skin test and adult asthma severity (*P* = .20-.45). Also, type of allergen sensitivity (indoor vs outdoor) and change in skin test sensitivity to a particular allergen from childhood to adulthood were not associated with adult severity (data not shown).

Adult factors and current asthma severity

As adults, subjects in remission had fewer positive skin tests from a panel of 18 allergy skin prick tests than subjects with intermittent or persistent asthma (6 vs 9 vs 9; *P* = .04). Other variables, including total IgE level, smoking status, and eczema and rhinitis symptoms, were not associated with current asthma severity.

TABLE IV. Relationship of childhood asthma and atopy status to adult asthma severity*

	Remission (N = 13)	Intermittent (N = 19)	Persistent (N = 53)	P
Age, y				
Age at onset (range)	4 (1-8)	2 (1-6)	3 (0-8)	.13
Age at follow-up (range)	23 (19-28)	22 (17-29)	23 (18-30)	.14
Sex (% male)	10 (76.9%)	17 (89.4%)	35 (66.0%)	.13
Race				
White	9 (69.2%)	11 (57.9%)	26 (49.1%)	.69
African American	4 (30.8%)	8 (42.1%)	26 (49.1%)	
Other	—	—	1 (1.8%)	
Active immunotherapy (% treatment)	6 (46.2%)	12 (63.2%)	25 (47.1%)	.46
Total serum IgE (ng/mL)†	412 (236-721)	1136 (716-1803)	968 (703-1332)	.02
Allergy skin testing‡	7 (5-9)	9 (8-11)	10 (9-11)	.02
Average daily asthma medication usage during clinical trial§	1.6 ± 2.3	3.5 ± 2.6	4.4 ± 2.3	.005
Mean % days on inhaled corticosteroids during immunotherapy trial	13.7%	24.7%	39.8%	.005
FEV ₁ % predicted at randomization	93.2 ± 15.9	93.7 ± 15.4	86.7 ± 13.1	.12
FEV ₁ /FVC % predicted at randomization	95.4 ± 6.4	93.1 ± 9.5	91.3 ± 10	.35
Average peak flow (% predicted) during clinical trial	83.5 ± 6.9	85.3 ± 10.1	82.7 ± 13.0	.70
Methacholine FEV ₁ PC ₂₀ at randomization†	0.23 (0.14-0.38)	0.24 (0.18-0.32)	0.22 (0.18-0.26)	.51

*Remission defined as subjects in asymptomatic category; intermittent defined as subjects in mild, intermittent asthma category; persistent defined as subjects in mild, moderate, and severe persistent asthma categories.

†Geometric mean and 95% CI.

‡Mean number of positive allergy skin prick tests out of panel of 18; 95% CI.

§Daily medication usage score (range, 0-7), as previously described.⁴

||Prebronchodilator mean ± SD.

TABLE V. Early risk factors and exposures by adult asthma severity*

	Remission (N = 13)	Intermittent (N = 19)	Persistent (N = 53)	P
Prematurity (<34 wk gestation)	1 (7.7%)	1 (5.3%)	7 (13.2%)	.54
Breathing problems as newborn	1 (7.7%)	4 (21.0%)	12 (23.5%)	.45
Breast-fed	6 (46.2%)	11 (57.9%)	29 (56.9%)	.76
Cat and/or dog in home before 1 y old	5 (38.5%)	3 (15.8%)	17 (33.3%)	.28
Other children <12 y old in household	4 (30.8%)	8 (42.1%)	22 (43.1%)	.72
Secondhand tobacco smoke exposure	5 (38.5%)	8 (42.1%)	20 (39.2%)	.97
First-degree relatives with asthma	6 (46.2%)	13 (68.4%)	38 (73.1%)	.18

*Pearson χ^2 P values calculated across 3 adult asthma severity groups.

Asthma severity in relation to stature and BMI

Differences in percentile height, adjusted for gender and age, were noted between subject groups (Fig 2, A). Differences at the end of the original clinical trial were statistically significant ($P = .006$), but were no longer observed by early adulthood. Height at the start of the childhood trial correlated negatively with inhaled corticosteroid use during the trial ($r = -0.27$; $P = .02$; $n = 85$). No other significant correlations were noted between height and inhaled or oral corticosteroid use. Comparison of BMI in childhood and adulthood did not reveal significant differences, although the remission group tended to have higher BMI at each time point (Fig 2, B). For male subjects ($N = 63$) in the remission, intermittent, and persistent categories, mean adult height in centimeters was 180.3 cm versus 178.4 cm versus 176.3 cm, respectively ($P = .16$). For female subjects ($N = 22$), adult height was 170.2 cm vs 164.9 cm vs 160.6 cm, respectively ($P = .24$).

DISCUSSION

In this study, we assessed the severity of current asthma in a cohort of young adults with a history of moderate to severe childhood allergic asthma. After an average follow-up interval of 10.8 years (range, 8-15.6 years), a subset (15.3%; $N = 13$) are in remission despite the severity of their childhood disease. Another group (22.4%; $N = 19$) have mild, intermittent symptoms, and the remaining $\frac{2}{3}$ (62.4%; $N = 53$) continue to have mild, moderate, or severe persistent disease. Because the original cohort members all had moderate to severe disease with persistent symptoms for longer than 1 year before enrollment, more than $\frac{1}{3}$ (37.6%; $N = 32$) demonstrated improvement from their level of childhood asthma severity.

The majority, however, continues to have persistent disease. This relatively high rate of persistence may reflect the selection of relatively severe asthma in the original cohort. Using minimized medication usage (averaged over a period of 3 years of observation) as an index of

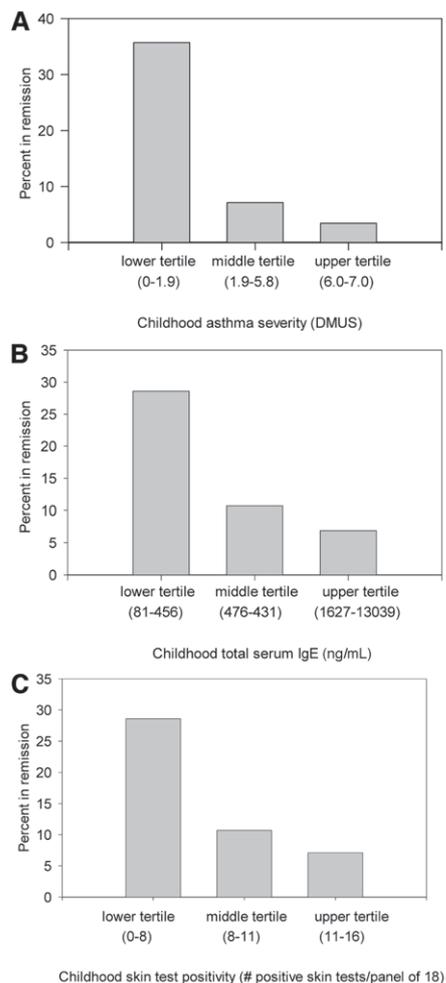


FIG 1. Remission rates by childhood severity. Cohort divided into tertiles of (A) average daily asthma medication usage score (DMUS)⁴ during clinical trial ($P = .001$); (B) total serum IgE ($P = .05$); and (C) number of positive allergy skin tests in childhood ($P = .06$).

childhood disease severity, average medication requirements strongly predicted adult severity. Subjects with the lowest asthma medication requirements in childhood had markedly higher rates of remission compared with those with the highest medication usage (35.7% vs 3.4%; $P = .001$; Fig 1, A). Studies in children with less severe disease have reported a similar association between childhood and adult severity.^{3,13} The Melbourne Asthma Study, consisting of 331 children with varying degrees of wheezing and asthma, found that nearly half of the subjects with the most severe symptoms at age 7 years had persistent, severe symptoms at age 21 years.³ At age 42 years, only 8 (9.6%) of the 83 subjects with severe childhood asthma were in remission, with an additional 5 (6.0%) reporting infrequent symptoms. Likewise, in a Dutch asthma cohort ($N = 46$; age 8-12 years), disease persistence in early adulthood (mean age, 24.7 years) was associated with childhood symptom severity.¹³

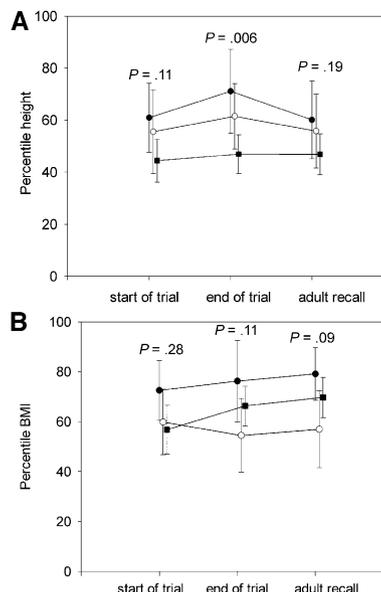


FIG 2. Mean (A) height and (B) BMI percentiles from childhood to adulthood. Repeated-measures ANOVA showed no significant time-asthma severity interactions for either height or BMI, so trends in the remission, intermittent, and persistent asthma groups are similar. Error bars indicate 95% CIs. ●, Remission; ○, intermittent; ■, persistent.

A relationship between childhood atopy and asthma development and persistence has been previously suggested by other studies. In a British birth cohort, Rhodes et al¹⁴ reported an association between sensitivity to egg, milk, or both during the first year of life and adult asthma (odds ratio, 10.7; 95% CI, 2.1-55.1; $P = .001$). Higher total serum IgE at age 3 years and 11 years was also associated with adult asthma. In the Dunedin, New Zealand, cohort, sensitization to house dust mites at age 13 years predicted persistent wheezing at age 26 years (odds ratio, 2.41; $P = .001$).² In our study, we observed that the overall atopic burden may be more critical to the persistence of asthma than a particular allergen, as suggested by the increased adult disease severity seen with increasing number of positive allergy skin tests and total serum IgE. Although patterns of allergen sensitization may vary with local environment, the degree of overall atopy may predispose certain individuals to chronic airway inflammation and airway remodeling, leading to disease persistence. Notably, no associations were seen between childhood immunotherapy status and adult asthma severity. It may be that immunotherapy must be initiated at a much earlier stage of allergen sensitization to influence asthma development, although pinpointing the appropriate time for intervention may be difficult.¹⁵ In addition, we did not observe an association between asthma severity and smoking history, although this result is likely confounded by smoking avoidance in subjects with more symptomatic disease.

A relationship between early allergen exposures and development of childhood disease has been reported by others,¹⁶ but an association between early exposure levels and persistence of childhood disease into adulthood has not been established. In our cohort, no statistically significant associations were found between specific childhood allergen exposure levels in subjects with a positive skin test and later adult asthma severity. The power of this analysis is limited by a relatively small sample size for individual allergen sensitivities. Other study limitations include the uncertain reliability of subjects' self-reports as well as the difficulty in quantifying certain exposures, such as breast-feeding or second-hand tobacco smoke. In addition, there remains the possibility that the subjects evaluated in adulthood may differ from those not evaluated in ways that we cannot ascertain.

In our study, subjects with milder asthma tended to be taller. The height difference was statistically significant near the end of the original clinical trial, coinciding with early adolescence for most of the subjects. The usual pubertal growth spurt may have accentuated small growth differences between patients with more severe asthma and patients with milder disease. The observed height gap may be a result of an early, steroid-induced attenuation of growth velocity or may be secondary to asthmatic inflammation itself. A modest negative correlation between inhaled corticosteroid use and percentile height existed only at the start of the original clinical trial ($r = -0.27$; $P = .02$). No other significant correlations between stature and oral and/or inhaled corticosteroid usage in childhood were observed, consistent with previous published studies.^{17,18}

In summary, we conclude that the degree of atopy is a major determinant of the prognosis of childhood allergic asthma in adulthood. In our cohort, adult asthma severity was associated with childhood disease severity and indices of atopy, suggesting that adult outcomes are decided at a very young age. By the time a child requires medical treatment, the course of disease may already be established. As a result, any attempts to alter the prognosis of childhood asthma are most likely to be effective when directed at the earliest stages of disease. Elucidating the development of atopy and its interplay with environmental exposures and heredity will facilitate improved understanding of outcomes and disease prevention.

REFERENCES

- Gerritsen J, Koeter GH, Postma DS, Schouten JP, van Aalderen WM, Knol K. Airway responsiveness in childhood as a predictor of the outcome of asthma in adulthood. *Am Rev Respir Dis* 1991;143:1468-9.
- Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
- Horak E, Lanigan A, Roberts M, Welsh L, Wilson J, Carlin JB, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. *BMJ* 2003;326:422-3.
- Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
- National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health; 1997. Publication 97-4051.
- Enright PL, Lebowitz MD, Cockcroft DW. Physiologic measures: pulmonary function tests: asthma outcome. *Am J Respir Crit Care Med* 1994;149:S9-18.
- Kuczumarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 2002;11:1-190.
- Lung function testing: selection of reference values and interpretational strategies: a statement of the American Thoracic Society. *Am Rev Respir Dis* 1991;144:1202.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- Huss K, Adkinson NF Jr, Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2001;107:48-54.
- Limb SL, Brown KC, Wood RA, Wise RA, Eggleston PA, Tonascia J, et al. Irreversible lung function deficits in young adults with a history of childhood asthma. Manuscript submitted.
- Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF Jr. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. *J Allergy Clin Immunol* 1996;97:1393-401.
- Roord RJ, Gerritsen J, Van Aalderen WM, Schouten JP, Veltman JC, Weiss ST, et al. Risk factors for the persistence of respiratory symptoms in childhood asthma. *Am Rev Respir Dis* 1993;148:1490-5.
- Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001;108:720-5.
- Liu AH. Consider the child: how early should we treat? *J Allergy Clin Immunol* 2004;113(suppl):S19-24.
- Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood: a prospective study. *N Engl J Med* 1990;323:502-7.
- Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343:1064-9.
- Norjavaara E, Gerhardsson De Verdier M, Lindmark B. Reduced height in Swedish men with asthma at the age of conscription for military service. *J Pediatr* 2000;137:25-9.